Remarks

A. Status of the Claims

Claims 29, 31–38, 47, and 57–58 were pending at the time of the Action. Claims 29 and 47 are currently amended. New claims 59 and 60 have been added. No new matter was added by these amendments. Thus, claims 29, 31–38, 47, and 57–60 are currently pending.

B. Objection to the Drawings

The Action objects to the italics used in FIGs. 1B and 2B. Applicants have removed the italics in FIG. 1B, as well as in FIG. 2B. Applicants respectfully request the withdrawal of this objection in view of the amendment to the drawings submitted herewith.

C. Objections to the Specification

The Specification is objected to because the heading "Brief Description of the Drawings" is not present. Applicants respectfully request the withdrawal of this objection in view of the amendments to the specification submitted herewith.

At page 27, the Action states that it maintains a prior objection to the specification on the basis that the title of the invention is not descriptive and because Applicants did not amend the title. Applicants note that their Amendment and Response dated March 18, 2009, amended the title of the application. Thus, Applicants respectfully request that those amendments be entered and that this objection to the specification be withdrawn.

D. Claim Objections

The Action objects to claim 47 as containing a typographical error. In light of Applicants' claim amendments submitted herewith, Applicants respectfully request the withdrawal of this objection.

E. Enablement Rejections

The Action rejects claims 29, 31–38, 47, and 57–58 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Specifically, the Action states that the claims encompass the following methods: (1) methods in which antibody binding is used to determine whether proBNP is present in the sample as well as whether fragments of proBNP are present in the sample; and (2) methods in which the concentration of canine proBNP as well as the concentration of fragments of proBNP are determined. Action at 5–6. Thus, the Action reasons that the claims lack enablement because the specification does not teach how to distinguish proBNP from its fragments. Action at 6. Specifically, the Action states:

> Absent direct guidance with regard to how to distinguish proBNP from such fragments by the disclosed immunoassay methods, the specification fails to teach the skilled artisan how to carry out the claimed invention in its full scope, as simply assessing the amount of antibody binding would not be sufficient to distinguish proBNP from its fragments or to separately determine the concentrations of proBNP or its fragments.

Action at 7–8.

To obviate this aspect of the rejection, the Action suggests that the claims be amended to recite a method of "determining canine proBNP or fragments thereof" in the preamble and conclude with the step of "determining the presence and/or concentration of canine proBNP or fragments thereof." Action at 29. Applicants disagree that the claimed methods require the ability to distinguish between a full-length proBNP and a fragment of proBNP. Applicants' working examples demonstrate that the disclosed methods allow one to distinguish a healthy canine from a canine that is suffering from heart disease without separately determining whether the sample contained pro-BNP, a fragment of pro-BNP, or a mixture of both. *See* Example 3 at

pages 12–13. Nonetheless, Applicants have amended the claims as suggested by the Examiner. Thus, Applicants respectfully request withdrawal of this rejection..

F. Indefiniteness Rejections

The Action rejects claims 29, 32–38, 47, and 58 under 35. U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Action alleges that there is not enough information in the specification to uniquely identify amino acids 20–86 of canine proBNP. Action at 8. Applicants respectfully traverse.

As the Action notes, Figure 1B provides amino acid sequences for specified epitopes present in canine proBNP. In addition, the specification discloses that the amino acid sequence of canine proBNP is published in Swiss-Prot Accession No. P16859. The Action alleges that one of ordinary skill in this art would be unable to use that information to identify which amino acids are encompassed by Applicants' claims regarding amino acids 20–86 of canine proBNP. Applicants disagree.

Figure 1B unambiguously indicates which amino acid Applicants regard as amino acid 20 and which amino acid Applicants regard as amino acid 86. Specifically, from Figure 1B, it can be seen that amino acid 20 is a valine and amino acid 86 is a methionine. One can then look to the sequence published in Swiss-Prot Accession No. P16859 and identify the corresponding valine and methionine. One could then determine the entire amino acid sequence encompassed by Applicants' claims regarding amino acids 20–86. Because one of ordinary skill in the art would be able to identify amino acids 20 to 86 of canine proBNP in light of the specification, the claims are definite, and withdrawal of this rejection is respectfully requested.

The Action reasons that Applicants' reliance on the database sequence information is inappropriate because the specification has not effectively incorporated by reference the database

amino acid sequence information. Action at 30. Applicants respectfully disagree. As explained above, the relationship between the sequences recited in the specification and the sequence recited in P16859 would not be ambiguous to a person of ordinary skill in the art. Accordingly, the recitation of a full-length proBNP sequence in the specification is not essential. Moreover, there is no *per se* rule that an invention that involves a biological macromolecule must contain a recitation of the molecule's known structure in order to adequately describe the invention. *See Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006). In addition, it is well established that a patent need not teach, and preferably omits, what is well known in the art. *See Hybridtech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1987). It is, therefore, unnecessary to reproduce the entire amino acid sequence of canine proBNP in the specification when a publicly accessible source, which is identified in the specification, provides the sequence.

G. The Rejections Under 35 U.S.C. § 103(a)

The Action rejects all claims under 35 U.S.C. § 103(a) as allegedly obvious over the cited references.

1. Rejections over MacDonald in view of Asada, Harlow & Lane, Janeway, and Wolfe

The Action rejects claims 29, 31–33, 37–38, 47, and 57–58 as allegedly obvious over MacDonald in view of Asada *et al.*, Harlow & Lane, Janeway *et al.*, and Wolfe. MacDonald is said to disclose a positive correlation between BNP-32 levels and cardiac disease in canines. Asada is said to teach that it is indispensable to assay both BNP-32 and pro-BNP in order to accurately diagnose cardiac disease. The Action acknowledges that Asada's example involved human BNP sequences, but the Action asserts that Asada "clearly contemplates" any mammalian proBNP including canine proBNP. The Action, therefore, concludes that it would have been

obvious to modify the method of MacDonald to detect not only canine BNP-32 but also proBNP in order to obtain more accurate results. The remaining publications by Harlow & Lane, Janeway *et al.*, and Wolfe are cited for their teachings with respect to antibodies generally. Applicants traverse this rejection.

To establish a *prima facie* case of obviousness the Action must, among other things, establish that there would have been a reasonable expectation of success to achieve the claimed invention. A reasonable expectation of success has not been established in this case because of several unpredictable factors. It was not previously known which fragments of canine proBNP circulated in blood or whether any such fragments were sufficiently abundant or stable to be detected by immunoassay. Asada reported that ***human*** BNP exists primarily in human blood as proBNP rather than BNP-32. Asada does not, however, disclose which form of ***canine*** BNP is predominant in canine blood. The Action merely speculates that Asada's findings concerning human BNP would apply to canines. As the Declaration of Dr. Adrian Boswood[1] explains, which is attached as Appendix A, such speculation is improper in this case. As explained below, based on the unpredictability and uncertainty surrounding BNP as of September 8, 2004, it was not possible to predict that one could detect canine proBNP in blood or urine based on teachings regarding detection of human proBNP. *See* Declaration of Adrian Boswood, Appendix A, ¶¶ 19–20.

[1] Biomedica Medizinprodukte GmbH & Co. is the owner of the claimed intellectual property, and Idexx Laboratories, Inc., is a licensee of that intellectual property. Dr. Boswood is not employed by Biomedica or Idexx. However, Biomedica paid Dr. Boswood £ 500.00 for four hours of time that he spent on this declaration. Also, in 2009, Dr. Boswood's lab received $10,000 in grant funds from Idexx. Idexx also provided NT-proBNP test kits to Dr. Boswood's lab. This information is being disclosed to comply with Applicants' duty to disclose information under 37 C.F.R. § 1.56 to the U.S. Patent Office. *See, e.g., Ferring B.V. v. Barr Labs, Inc.*, 437 F.3d 1181 (Fed. Cir. 2006).

a) Uncertainty surrounding forms of proBNP in humans

The Boswood Declaration explains, at ¶ 4, that although some information regarding the forms of BNP present in human tissues and in blood was known, much remained unknown about human BNP molecules. In other species, namely cats and dogs, less was known about BNPs in general and proBNP specifically. Appendix A, ¶ 3.

Regarding human BNP forms, studies indicated that there were yet unidentified proBNP forms circulating in human plasma. Appendix A, ¶ 4. For example, some proBNP molecules exhibited a much higher molecular weight than would be expected for a single proBNP molecule, indicating that BNPs may bind to other molecules or to each other. Appendix A, ¶ 4 (citing Goetze, Biochemistry of Pro-B-Type Natriuretic Peptide-Derived Peptides: The Endocrine Heart Revisited, *Clin. Chem.* **50:**1503–10, 2004, IDS Reference C14 ("Goetze")). The Declaration notes that the authors of the Goetze 2004 review article concluded:

> Thus, although proBNP and its N-terminal fragments seem to associate to something in cardiac tissue and plasma, the underlying mechanism still needs to be determined. It is nevertheless important to emphasize that such oligomerization may have a major influence on antibody detection and assay performance.

Appendix A, ¶ 4.

Thus, as of 2004, it was unknown how many forms of BNP molecules are circulating in human plasma. Appendix A, ¶ 5. Moreover, because "proBNP and its N-terminal fragments seem to associate to something in cardiac tissue and plasma," it was not possible to predict that an antibody against a particular amino acid region of proBNP could detect proBNP or a particular N-terminal fragment of proBNP. Appendix A, ¶ 5. In canines, as compared to humans, less was known about BNPs generally and about proBNP specifically. Appendix A, ¶ 3. Thus, based on the uncertainty regarding the forms of human proBNP circulating in human

blood as of September 8, 2004, it was not possible to predict that canine proBNP was present in canine blood or urine and could be detected using antibodies.

In this case, no cited reference discloses any teachings regarding proBNP in canines. Due to the uncertainty regarding proBNP in general, and canine proBNP specifically, it was not possible to predict that a protein that could be detected by antibodies in human blood would be sufficiently abundant and stable to be detected in canine blood or urine. Moreover, even if circulating canine proBNP was present, it was unpredictable whether a particular region of canine proBNP would be accessible due to factors such as oligomerization of the protein or cleavage of certain regions during BNP processing.

b) Uncertainty surrounding BNP forms in canines

The Action alleges that it would have been obvious to detect proBNP in canine blood based on studies that detected proBNP in human blood. Applicants respectfully disagree. As the Boswood Declaration explains, although it was reported that human BNP exists primarily in human blood as proBNP, it remained unknown in September 2004 how many forms of BNP are present in other species, such as canines, and which of those BNP forms would predominate in the plasma in those species. Appendix A, ¶ 8. In fact, the Boswood Declaration explains that growing evidence indicated that the forms of BNPs present in blood and tissues, as well as the functions of BNPs, varied across species. Appendix A, ¶ 8. Because the cited references do not provide any teachings regarding proBNP in canines, and because the prior art teaches that BNP molecules vary across species, one of skill in this art would have recognized that it was not possible to predict that canine proBNP could be detected in canine blood or urine using an antibody directed against amino acids 20-86 of canine proBNP.

As one study published in 2002 explained: "[P]reproBNP of eight mammalian species showed variations in length and sequence structures. This supports the species-specific actions of BNP across species." Appendix A, ¶ 9 (citing Liu *et al.*, Cloning and Characterization of Feline Brain Natriuretic Peptide, *Gene* **292:**183–90, 2002, at p. 188, col. 2 (IDS Reference C6, "Liu")). Comparing BNP sequences across species, the authors of that study grouped the species as follows: (a) rat and mouse BNPs are closely related; (b) cattle, sheep, and swine BNPs are closely related; (c) cat and dog BNPs are closely related; and (d) human BNP is in a "distinct group as compared to the other species." Appendix A, ¶ 9. Regarding human BNP, the authors specifically noted that "human preprop[e]ptide has many unique sequences and appears to have evolved independently from other species." Appendix A, ¶ 9. Thus, this study indicates that studies regarding BNP in humans would not predictably translate to BNP in dogs.

Another study also noted the structural variation of BNPs across species:

> BNP differs across species, with only short segments retaining sequence homology. In addition, there are species-specific variations in the structure of the non-guanylyl cyclase-linked natriuretic peptide C (NP_C) receptor or clearance receptor, <u>which is likely to affect the metabolism of BNP</u>.

Appendix A, ¶ 10 (citing Thomas *et al.*, Haemodynamic Action of B-Type Natriuretic Peptide Substantially Outlasts its Plasma Half Life in Conscious Dogs, *Clin. Exp. Pharmacol. Physiol.* **30:**369–75, 2003, at p. 369, col. 1 (IDS Reference C16, "Thomas") (emphasis added)). In particular, that study indicated the likelihood that BNP is metabolized differently across species. Appendix A, ¶ 10.

Studies performed by Giosi Farace at Idexx Laboratories, which is a licensee of the technology claimed in this application, demonstrate the variation in proBNP structure across species. *See* Declaration of Giosi Farace, Appendix B. Specifically, the studies performed by

Giosi Farace demonstrate that the amino-terminal regions of proBNP (NTproBNPs) differ structurally across species, and that antibodies directed against human, feline, or canine NTproBNP are species-specific. Appendix B, ¶¶ 2–6.

The Boswood Declaration explains that such structural heterogeneity of BNP molecules across species could have at least two consequences. Appendix A, ¶ 11. First, BNP could have different fragmentation patterns in different species. Appendix A, ¶ 11. Second, BNP forms could have different half-lives in different species. Appendix A, ¶ 11. Indeed, studies confirmed that BNP does have different fragmentation patterns across species, and the half-life of BNP molecules does vary across species. Appendix A, ¶ 11.

First, studies confirmed that one species may have different forms of BNP as compared to a different species. For instance, one 32-amino-acid form of mature BNP was known in human, dog, and pig; one 45-amino-acid form of mature BNP was known in mouse and rat; two forms of mature BNP were known in sheep (one form having 26 amino acids and one form having 29 amino acids); two forms of mature BNP were predicted in cow (one form having 26 amino acids and one form having 29 amino acids); and three forms of mature BNP were predicted in cat (one form having 26 amino acids, one form having 29 amino acids, and one form having 35 amino acids). Appendix A, ¶ 12. Thus, it was known that one species may have different forms of circulating BNPs as compared to a different species. Appendix A, ¶ 12.

Second, studies confirmed that the half-life of BNP molecules varies across species. For example, studies showed that the half-life of canine BNP is far shorter than the half-life of BNP in rats, sheep, or humans. Appendix A, ¶ 13. Thus, it was known that the stability of BNP molecules varies across species. Appendix A, ¶ 13. Specifically, it was known that the stability of BNP molecules varies in canines as compared to humans.

For these reasons, based on the uncertainty and unpredictability surrounding BNPs as of September 8, 2004, the Boswood Declaration explains that it was not possible to predict how many forms of BNP were present in canine blood, which forms of circulating BNP would be predominant in canines, or whether such forms of circulating BNP would be stable enough to be detected by antibodies in canines. Appendix A, ¶ 19. Thus, it was not possible to predict whether canine proBNP could be detected in canine blood or urine. *See* Appendix A, ¶ 20 ("[I]t was unknown whether circulating proBNP could be detected in dogs or cats.").

None of the cited references overcomes this unpredictability. Asada is cited as teaching the detection of human proBNP, and Harlow & Lane, Janeway *et al.*, and Wolfe are cited for their teachings with respect to antibodies generally. Thus, the cited references do not provide teachings that would overcome the unpredictability of detecting canine proBNP in blood or urine.

The current claims are patentable over MacDonald, Asada, Harlow & Lane, Janeway, and Wolfe for at least the reasons discussed above. Applicants, therefore, request the withdrawal of this rejection.

2. Rejections over MacDonald in view of Asada, Harlow & Lane, Janeway, Wolfe, and Harlow & Lane 2

Dependent claims 34-36 are rejected as allegedly unpatentable over the MacDonald, Asada, Harlow & Lane, Janeway, and Wolfe references discussed above, further in view of Harlow & Lane 2. Applicants traverse this rejection.

If an independent claim is nonobvious under 35 U.S.C. § 103(a), then any claim depending therefrom is nonobvious. MPEP § 2143.03. For the reasons discussed in the preceding section, claims 29, 31-33, 37-38, 47, and 57-58 are non-obvious over MacDonald,

Asada, Harlow & Lane, Janeway, and Wolfe. Thus, dependent claims 34-36 are also non-obvious.

3. Rejections over MacDonald in view of Karl and Liu

Claims 29, 31-38, 47, and 57-58 are rejected as allegedly unpatentable over MacDonald in view of Karl *et al.* and Liu *et al.* The Action alleges that it would have been obvious to modify the method of MacDonald to detect NT-proBNP instead of BNP-32 in view of the teachings of Karl. Liu is cited as teaching that canine BNP sequences were known and are similar to those from other species. Liu is also cited to support the Action's assertion that with knowledge of a protein's amino acid sequence, antibodies can be produced against the protein in order to detect the protein by clinical immunoassay. Applicants traverse this rejection.

As mentioned above, to establish a *prima facie* case of obviousness the Action must, among other things, establish that there would have been a reasonable expectation of success to achieve the claimed invention. A reasonable expectation of success has not been established in this case because of several unpredictable factors. As explained in detail above, and in the Declaration of Dr. Adrian Boswood, it was not previously known which fragments of canine proBNP circulated in blood or whether any such fragments were sufficiently abundant and stable to be detected by immunoassay. Karl reported that ***human*** BNP is more stable than BNP-32. Karl does not, however, discuss the stability of ***canine*** BNP or BNP-32. The Action merely speculates that Karl's findings concerning human BNP would apply to canines. As discussed above, and in Dr. Boswood's Declaration, such speculation is improper in light of the unpredictability and uncertainty surrounding BNP as of September 8, 2004.

H. Double Patenting Rejection

Claims 29, 31-38, 47, and 57-58 are provisionally rejected for obviousness-type double patenting over claims 1-20 of co-pending Application No. 12/394,731. A provisional double-patenting rejection is not a final rejection that blocks the prosecution of all of the conflicting applications. If a provisional double-patenting rejection is the only rejection remaining in the earlier filed application, the Examiner should withdraw the rejection and permit the application to issue as a patent without a terminal disclaimer. MPEP § 804(I)(B).

I. Conclusion

Applicants believe this to be a complete response to all issues raised in the Final Office Action dated November 19, 2009. The Examiner is invited to contact the undersigned attorney at (512) 536-5654 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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